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EXAMINER	
WANG, CHANG YU	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/512,004	TZARTOS ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,14-16,18-26 and 28-42* is/are pending in the application.

4a) Of the above claim(s) *28-35,37 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 14-16, 18-26, 36 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed 4/20/09 is acknowledged. Claims 1-10, 12-13, 17, and 27 are cancelled. Claims 11, 14-16, 18-26 and 36 are amended. Claim 42 is newly added. Claims 11, 14-16, 18-26, 28-41 and newly added claim 42 are pending in this application. Claims 28-35, 37 and 41 are withdrawn with traverse (the response filed on 7/14/08) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/14/08.

2. Claims 11, 14-16, 18-26, 36 and 42 are under examination in this office action.

3. Any objection or rejection of record, which is not expressly repeated in this office action has been overcome by Applicant's response.

4. Applicant's arguments filed on 4/20/09 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

6. The objection to the title is withdrawn in response to Applicant's amendment to the title.

Claim Rejections/Objections Withdrawn

7. The rejection of claims 11-27 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 12-13, 17, and 27.

The rejection of claims 16, 18-22 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements is withdrawn in response to Applicant's arguments.

The rejection of claims 11-27 under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 12-13, 17, and 27.

The rejection of claims 11-21, 23-27 and 36 under 35 U.S.C. 102 (a) as being anticipated by Psaridi-Linardaki et al. (J. Biol.Chem. 2002. July, 277:2698-26986) is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 12-13, 17, and 27.

The rejection of claims 11-18, 23 and 25-26 **u**nder 35 U.S.C. 102 (b) as being anticipated by Barchan et al. (Eur. J. Immunol.1998. 28: 616-624) is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 12-13, 17.

The rejection of claims 11-14, 17-18, 23, 25-27 and 36 under 35 U.S.C. 102 (b) as being anticipated by US Patent No. 5578496 (cited previously) is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 12-13, 17, and 27.

The rejection of claims 11-14, 17-23, 25-27 and 36 under 35 U.S.C. 102 (b) as being anticipated by Besson et al. (Neurology, 1996. 47:1552-1555) is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 12-13, 17, and 27.

Claim Rejections/Objections Maintained

In view of the amendment filed on 4/20/09, the following rejections are maintained.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16, 18-22 stand rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The rejection is maintained for the reasons made of record.

On p. 19-20 of the response, Applicant argues that the sequence of AChR is readily available through publications and sequence databases. Applicant further cites Schoepfer et al. (1987) and Beeson et al. (1990) for the alpha subunit of AChR, Besson

et al. (1989) for the beta subunit of AChR, Luther et al. (1989) for the delta subunit of AChR, Besson et al. (1993) for the gamma and epsilon subunits of AChR and Engel et al. (1996) for mutations in several subunits of AChR, and also cites the sequences of accession Nos. ACHA_HUMAN P02708 (alpha), ACHB_HUMAN P11230 (beta), ACHG_HUMAN P07510 (gamma), ACHD_HUMAN Q07001 (delta), ACHE_HUMAN Q04844 (epsilon) in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In response, the claims only recite "the alpha/beta/gamma/delta/epsilon subunit comprises amino acids 1-210/1-222/1-218/1-224/1-219", which is not clear what specific sequences Applicant intended to use or refer to. For example, the recitation of "comprising amino acids 1-210" can be interpreted as comprising one amino acid to two hundred and ten amino acids derived from any sequence of the recited subunit molecule. The recitation can also be interpreted as comprising amino acid residues position 1 to position 210 of a specific amino acid sequence derived from the recited subunit. Thus, it is not clear what Applicant intended to use in the claimed method and thus the claims are indefinite.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 14-16, 18-26, 36 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons made of record.

On p. 21-22 of the response, Applicant argues that the instant claims meet the written description because the claims have been recited "the N-terminal extracellular domain the molecule" and the instant specification have taught how to assay the ability of N-terminal extracellular domain (amino acid 1-210) of the alpha subunit in Example 1 and also show the detailed expression of the extraceullar domains of beta, gamma, delta and epsilon subunits and their purification and characterization in Example 2 and also discloses immunoadsorption of antibodies from MG patients' sera with a combination of subunits in Example 3. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, although the general sequence of AChR subunits are known in the art, the limitation of "the N-terminal extracellular domain of the alpha/beta/gamma/delta/epsilon subunit comprises amino acids 1-210/1-222/1-218/1-224/1-219" are not limited to the sequences as shown in the specification or as shown on p. 19-20 of the response filed 4/20/09. In addition, claims 15-16 are directed to mutant forms of the AChR subunits. However, the specification fails to teach what common specific structure, features or amino acid sequences are required by the

claimed subunits and mutant forms. In addition, the limitation of "the N-terminal extracellular domain of the alpha/beta/gamma/delta/epsilon subunit comprises amino acids 1-210/1-222/1-218/1-224/1-219" can be derived from any amino acid sequence that have 1-210/1-222/1-218/1-224/1-219 amino acids in length. However, the specification also fails to teach what specific sequences or structures are required by the claimed subunits and mutants and thus can be used in the claimed method. Note that

A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. See also *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen Inc. v.Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle &Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

Accordingly, the court held in *Univ. California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) that:

"One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is".

and that:

"A description of a genus of cDNAs [products] may be achieved by means of a recitation of a representative number of cDNAs [products], *defined by nucleotide sequence*, failing in the scope of the genus or of a recitation of structural features common to the members of the genus, *which features constitute a substantial portion of the genus* [emphasis added]. This is analogous to enablement of a genus under 112, [first paragraph], by showing the enablement of a representative number of species within the genus. See *In re* Angstadt, 537 F.2d at 502-03, 190 USPQ at 218".

In contrast, the specification provides an invitation for others to discover a representative number of species, or to discover what constitutes any particular portion of the structure that must be conserved, with a known or disclosed correlation between

function and structure, or by a combination of such identifying characteristics. Thus, Applicants were not reasonably in possession of the claimed genus of subunits and the mutants that can be used in the claimed method.

New Grounds of Rejection Necessitated by the Amendment

The following rejections are new grounds of rejections necessitated by the amendment filed on 4/20/09.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 14-16, 18-26, 36 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Psaridi-Linardaki et al. (J. Biol.Chem. 2002. July, 277:2698-26986, cited previously) in view of Barchan et al. (Eur. J. Immunol.1998. 28: 616-624, cited previously), and Besson et al. (Neurology, 1996. 47:1552-1555, cited previously).

Claims 11, 14-16, 18-26, 36 and 42 as amended are drawn to a method of immunoadsorption of anti-AChR antibodies by using a combination of recombinant N-terminal extracellular domains of alpha, beta, gamma, delta and epsilon subunits of a primate muscle nicotinic acetylcholine receptor (AChR), wherein the recombinant N-terminal extracellular domains are mutant forms of the domains including substitutions of free cysteine by other amino acids or substitutions of the hydrophobic loops of the subunits 128-142 or alpha domain of containing P3A axon or a FLA tag at the N-terminus (claims 15 and 16) and wherein the recombinant domains are expressed in an eukaryotic expression system selected from the group consisting of Pichia pastoris, Semilik Forest Virus and combination thereof .

Psaridi-Linardaki et al. teach a method of immunoadsorption of anti-AChR antibodies of myasthenia gravis (MG) patients using a combination comprising a recombinant domain of amino acid residues 1-210 of human alpha subunit (human

alpha 1-210) in combination with a combination comprising a solubilized hybrid AChR HαTβγδ containing human α and Torpedo β, γ and δ subunits (see p. 26984, 1st -2nd cols., in particular). The recombinant domains of the human alpha 1-210 and the solubilized hybrid meet the limitations of a combination comprising different subunits that contain the N-terminal extracellular domain comprising recited amino acids of α, β, γ and δ subunits as in instant claims 11, 14, 17-21, 25, 26 and 42 (see p. 26984, 1st -2nd col., in particular). In addition, Psaridi-Linardaki et al. teach the recombinant domains are expressed in yeast Pichia pastoris expression system as recited in instant claims 23-24 and 26 (see p. 26981, 1st col., 4th paragraph, in particular). Furthermore, Psaridi-Linardaki et al. teach removal of anti-AChR antibodies from the blood (i.e. serum) of MG patients using the claimed recombinant domains as recited in instant claims 27 and 36 (see p. 26981, 2nd col., 7th paragraph; p. 26984, 1st col., 3rd paragraph to col.2, 1st paragraph, in particular). But Psaridi-Linardaki et al. do not teach epsilon subunit as recited in claims 11, 22 and 36. In addition, Psaridi-Linardaki et al. do not teach that the recombinant domains are mutant forms of the domains including substitutions of free cysteine by other amino acids or substitutions of the hydrophobic loops of the subunits 128-142 or alpha domain of containing P3A axon or a FLA tag at the N-terminus as in claims 15 and 16.

Besson et al. teach a method of immunoadsorption of anti-AChR antibodies in the blood from MG patients using a combination comprising a recombinant domain of alpha, beta, gamma, delta, epsilon subunits of human AChR as recited in instant claims 11,14, 18-23, 25-26, 36 and 42 (see p. 2-3, in particular). Besson et al. teach that

recombinant domains of AChR subunits extracted from TE671-epsilon and TE671-gamma cell lines (see p. 2-3, in particular). The TE671-epsilon and TE671-gamma cell lines are TE671 cell lines that are transfected with AChR epsilon and gamma subunit respectively. TE671 cell lines also express AChR alpha, beta and delta subunits. Besson et al. also teach using the recombinant domains of different AChR subunits extracted from TE671-epsilon and –gamma cell lines for immunoadsorption of anti-AChR antibodies in the blood from MG patients, which meet the limitations as recited in the claims 27 and 36 (see p. 3-4). The recombinant domains of different AChR subunits comprise the N-terminal extracellular domain of each subunit and also comprise the recited amino acids as in claims 18-22. In addition, these recombinant domains are expressed in TE671 cell lines, which is a eukaryotic expression system and are also larger than 70 amino acids and comprises about 200 amino acids as recited in instant claims 23, 25-26 and 42.

Barchan et al. teaches a method of immunoadsorption of anti-AChR antibodies using a combination of recombinant domains from human alpha subunit Hα1-210 or Hα1-121 or Hα122-210, which meet the limitations of claims 11-14, 17, 18, 23, 25 and 26 (see p. 616, abstract; p.617, 2nd col. to p.619, 2nd col., in particular). Barchan et al. also teaches that the human alpha subunit exist two forms including 25-additional amino acid insertion between position 58 and 59 as encoded by exon p3A (see p. 617, 2nd col.; p. 620, 2nd col. to p. 621, 2nd col., in particular), which meets the limitations recited in instant claims 15-16.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to use a combination of recombinant N-terminal extracellular domains of alpha, beta, gamma, delta and epsilon subunits of a primate muscle AChR to remove anti–AChR antibodies from serum of a MG patient. The person of ordinary skill in the art would have been motivated to do so with an expectation of success because a combination of recombinant N-terminal extracellular domains of alpha, beta, gamma, delta and epsilon subunits of a primate muscle AChR has been successfully used to remove anti–AChR antibodies from serum of a MG patient as taught by Psaridi-Linardaki et al. and Besson et al.. In addition, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to use a combination of recombinant N-terminal extracellular domains of alpha, beta, gamma, delta and epsilon subunits of a primate muscle AChR to remove anti–AChR antibodies from serum of a MG patient wherein the recombinant domains are mutant forms of the domains include substitutions of free cysteine by other amino acids and substitutions of the hydrophobic loops of subunits corresponsing 128-142 by more hydrophilic sequence or alpha domain containing the P3A exon or a FLAG tag at the N-terminal in the presence or absence of the 6His tag. The person of ordinary skill in the art would have been motivated to do so with an expectation of success because a combination of recombinant N-terminal extracellular domains wherein the domains are mutants of claim 16 have been disclosed by Barchan et al. and used to remove anti-AChR antibodies as taught by Barchan et al.

Note that

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980); see also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992). See MPEP § 2144.06.

"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.,* 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

"Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)" See MPEP § 2143. 01-I.

Conclusion

11. NO CLAIM IS ALLOWED.

12. This application contains claims 28-41 drawn to an invention nonelected with traverse in the reply filed on 7/14/08. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
July 28, 2009

/Jeffrey Stucker/
Supervisory Patent Examiner, Art Unit 1649